

requirement. Claims 17, 19, 34, 52, 54, 72-74, 82, 83, 90, 91, 106, 107, 115-117, 119, 125, 141-143, 153-155, 162-164, 174-175, 196, and 197 are sought to be canceled without prejudice to or disclaimer of the subject matter thereof. Applicants reserve the right to pursue the subject matter of these claims in related applications. These changes are believed to introduce no new matter, and their entry is respectfully requested. Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

***Support for the Amendments***

The claims have been amended for clarity, and to more particularly point out and distinctly claim the subject matter Applicants regard as the invention. Applicants assert that the amendments requested herewith are to comply with requirements set forth in a previous office action. Furthermore, since the amendments and the following remarks are responsive to new rejections set forth in the previous Office Action (*i.e.*, Paper No. 12), they could not have been presented earlier. Finally, Applicants assert that these amendments present no new matter. Entry of these amendments is therefore respectfully requested.

***The Statement Concerning the Deposited cDNA Clone***

The Examiner has maintained a previous rejection under 35 U.S.C. § 112, first paragraph to those claims reciting ATCC Deposit No. 97853, stating that the executed Statement Concerning the Deposited cDNA clone did not accompany the Amendment and Reply filed on

November 23, 1999. *See* Paper No. 12 at page 8. This rejection pertains to pending claims 120-138.

Applicants respectfully maintain that a Statement Concerning the Deposited cDNA clone executed by James H. Davis was submitted with the Amendment and Reply filed on November 23, 1999. In support of this, attached hereto is a copy of the Statement Concerning the Deposited cDNA clone filed on November 23, 1999, as well as a copy of the stamped post-card receipt which lists this document as received by the P.T.O. on that date.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

#### ***The Restriction Requirement***

The Examiner has stated the claims 46, 66, 117, 137, 155, 176, 192, and 207 embody subject matter which is distinct from the invention originally claimed. *See* Paper No. 12 at page 2.

Claims 117, and 155 have been canceled. Applicants reserve the right to pursue the subject matter of these claims in related applications. With respect to claims 46, 66, 137, 176, 192, and 207, Applicants respectfully traverse, and submit that to search and examine the subject matter of these claims together with the remainder of the pending claims would not be a serious burden on the Examiner. For example, publications which disclose host cells comprising TNF-family receptors normally also disclose that such host cells are useful to screen for ligand binding, thereby making it a simple matter for the Examiner to search and examine a method to screen for ligand binding utilizing host cells of the present invention. The M.P.E.P. § 803 (Seventh Edition, Rev. July, 1998) states:

If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions.

Thus, in view of the M.P.E.P. § 803, Applicants respectfully request that claims 46, 66, 137, 176, 192, and 207 be searched and examined in the subject application.

Applicants retain the right to petition from the restriction requirement under 37 C.F.R. § 1.144.

However, while not acquiescing to the Examiner's restriction requirement, Applicants note that the claims 46, 66, 137, 176, 192, and 207 are related to the elected claims as between a product and a process for using the product, and further, that the process of claims 46, 66, 137, 176, 192, and 207 depend from and include all the limitations of the product of claims from which they depend, *i.e.*, claims 44, 65, 135, 172<sup>1</sup>, 190, and 205, respectively. In light of the decisions in *In re Ochiai*, 71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995) and *In re Brouwer*, 77 F.3d 422, 37 USPQ 2d 1663 (Fed. Cir. 1996), a notice was published in the Official Gazette which set forth new guidelines for the treatment of product and process claims. *See* 1184 OG 86 (March 26, 1996). Specifically, the notice states that

in the case of an elected product claim, rejoinder will be permitted when a product claim is found allowable and the withdrawn process claim depends from or otherwise includes all the limitations of an allowed product claim.

*Id.* Claim 190 has been allowed. Accordingly, Applicants respectfully request that claim 192 be rejoined and examined for patentability. Furthermore, Applicants respectfully request that if any

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<sup>1</sup>Claim 174, from which claim 176 currently depends, has been canceled. However, upon rejoinder, claim 176 would be amended to depend from claim 172.

of claims 44, 65, 135, 172, and 205 are found allowable, that claims 46, 66, 137, 176, and 207 be rejoined and examined for patentability.

***Rejection under 35 U.S.C. § 112, Second Paragraph***

(a) The Examiner has rejected claims 23, 34-36, 49, 52-54, 69, 72-74, 86, 89-91, 103, 106-107, 121, 125-127, 141, 159, 162, 194, and dependent claims 44, 45, 47, 64, 65, 57, 82-84, 99-101, 115, 116, 119, 135, 136, 138, 153, 154, 156, 163, 174, 175, 177, 195-206, and 208 under 35 U.S.C. § 112, second paragraph, alleging that the phrase "said nucleic acid" is indefinite, in that the independent claims refer to a nucleic acid and a "reference nucleic acid." *See* Paper No. 12 at page 3-4.

While not acquiescing to the Examiner's rejection, in order to expedite allowance of claims, Applicants have amended independent claims 22, 48, 68, 85, 102, and 120 to recite a "first" and a "second" nucleic acid, and have amended the corresponding dependent claims to refer back to either the "first" or "second" nucleic acids so named. Accordingly, Applicants respectfully request that this aspect of the rejection be reconsidered, and further that it be withdrawn.

(b) The Examiner has rejected those claims referring to "a TNF ligand" *i.e.*, claims 34, 52, 72, 90, 106, 125, 141, 162, and 194, under 35 U.S.C. § 112, second paragraph, stating that it is unclear what a TNF ligand is. *See* Paper No. 12 at page 4.

While not acquiescing to the Examiner's rejection, Applicants have canceled claims 34, 52, 72, 90, 106, 125, 141, and 162, and have amended claim 194 to refer to a polypeptide which binds TRAIL. Applicants reserve the right to pursue the canceled claims in related applications.

Accordingly, Applicants respectfully request that this aspect of the rejection be reconsidered, and further that it be withdrawn.

(c) The Examiner has rejected claim 159 under 35 U.S.C. § 112, second paragraph, alleging "it is unclear if the "nucleic acid" of the claim is intended to be the same as or in addition to the "nucleic acid" of claim 157, upon which it depends." *See* Paper No. 12 at page 4.

While not acquiescing to the Examiner's rejection, applications have amended claim 159 to recite "wherein said nucleic acid encodes amino acids 132 to 221 of SEQ ID NO:2." Accordingly, Applicants respectfully request that this aspect of the rejection be reconsidered, and further that it be withdrawn.

In view of these remarks, Applicants respectfully request that the Examiner reconsider and withdraw all rejections under 35 U.S.C. § 112, second paragraph, as applied to the pending claims.

***Rejections under 35 U.S.C. § 112, First Paragraph***

The Examiner has rejected "claims requiring the ability to encode a polypeptide that induces apoptosis or binds a TNF ligand or TRAIL and claims depending thereon . . . excluding claims 35-36, 126-127, and including claims dependent on claim 194 which are complementary to a coding sequence . . ." under 35 U.S.C. § 112, first paragraph. *See* Paper No. 12 at page 5. Further, the Examiner has rejected claims where the polynucleotide comprises "a nucleic acid at least 90% identical to a reference nucleic acid encoding a fragment of SEQ ID NO:2 where the fragment is not enabled or where the nucleic acid cannot be used commensurate in scope with the instant invention" under 35 U.S.C. § 112, first paragraph. *See Id.* The Examiner alleges that the

specification does not provide enablement for polynucleotides encoding less than the full extracellular domain that bind a TNF ligand or TRAIL or less than the full-length or mature polypeptide which induces apoptosis. *See* Paper No. 12 at page 4-7. In a telephonic interview with Applicants' representative Elizabeth J. Haanes on July 28, 2000, the Examiner further noted that claims directed to "a method to produce a polypeptide," *e.g.*, pending claims 47, 67, 84, 138, 156, 177, 193, and 208, are rejected for lack of enablement, apparently because applicants allegedly have not indicated the specific polypeptide to be produced, or its function.

The Examiner gives as examples of claims included in this portion of the rejection claims "34, 36, 44, 45, 47, 53-54, 64, 65, 67, 72-74, . . . 102-116, 118, 119, . . . 194 . . . , excluding claims 35-36, 126-127 . . . ." *See* Paper No. 12 at page 4. Based on these examples, Applicants have deduced that the claims the Examiner intends to include in this portion of the enablement rejection consist of claims 34, 44, 45, 47, 52-54, 64, 65, 67, 72-74, 82-84, 89-91, 99-101, 102-116, 118, 119, 125, 135, 136, 138, 141-143, 153, 154, 156, 162-164, 174, 175, 177, 193-206, and 208 only. If this is incorrect, a listing of the exact claims the Examiner intends to be included is respectfully requested. It is noted, however, that in the Office Action Summary, claim 34 is listed as being allowed, and it is not indicated whether claim 67 is rejected or allowed.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have canceled claims 34, 52, 54, 72-74, 82, 83, 90, 91, 106, 107, 115-117, 119, 125, 141-143, 153-155, 162-164, 174-175, 196, and 197, directed to polynucleotides with certain functional limitations, have amended claims 194 and 195 to specify that the claimed polynucleotide hybridizes to the complementary strand, and have amended claims 47, 67, 84, 138, 156, 177, 193, and 208, to specify a method of producing a polypeptide encoded by a claimed nucleic acid. With respect to the pending claims, as amended, Applicants respectfully traverse.

Under the Federal Circuit standard for enablement, some necessary experimentation by the skilled artisan is permitted; the amount of experimentation, however, must not be unduly extensive. *Atlas Powder Co. v. E. I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984). Furthermore, patent claims that include some claimed combinations which are inoperative are not necessarily invalid under 35 U.S.C. § 112. *Id.* As the Examiner has pointed out, factors to be considered when determining whether the amount of experimentation is undue were set out in *In re Wands*, 858 F.2d 731 at 737 (Fed. Cir. 1988). See Paper No. 12 at page 5.

The full extracellular domain of the DR4 polypeptide is described in the Specification to be amino acids 24 to 238 of SEQ ID NO:2. See the specification at page 10, lines 23-24. Accordingly, the full extracellular domain of the DR4 polypeptide is recited in claim 53. Claim 126, as amended, refers to a polynucleotide encoding the mature amino acid sequence encoded by the cDNA clone in ATCC Deposit No 97853 which has the ability to bind TRAIL. Claim 194, as amended, recites a polynucleotide comprising a nucleic acid which hybridizes to the complement of nucleotides 88 to 732 of SEQ ID NO:1, wherein the nucleic acid encodes a polypeptide which binds TRAIL. The Examiner has stated that the captioned application provides enablement for the full DR4 extracellular domain binding TRAIL. For support see *e.g.*, specification at page 8, lines 1-13 and Figure 6. Since each of claims 53, 126, and 194 recite certain polynucleotides which encode the full DR4 extracellular domain, claims 53, 126, and 194 each include specific embodiments which are enabled by disclosure of the present application.

Applicants further submit that claims 53, 126, and 194 are enabled for their full scope using the rule set out in *Atlas Powder* and *Wands*. Given (a) the teachings of the present application, and (b) the high level of skill in the art regarding TNF-family receptor/ligand interactions, one of ordinary skill in the art could routinely make and use polynucleotides

according to these claims which encode a polypeptide which binds TRAIL, without undue experimentation.

The specification teaches, at page 1, line 21 through page 4, line 2, and in the references cited therein, that a great deal is known about the ligand-binding domains of TNF-family receptors. For example, it is well known that specific conserved cysteine residues must be present for ligand binding to take place. Figure 2 shows a comparison of the amino acid sequences of four different TNF-family receptors, including DR4, which illustrates the conserved amino acids in the ligand binding extracellular domain important for TNF-family ligand binding activity. Accordingly, one of ordinary skill in the art could compare the deduced amino acid sequences of the ligand binding domains of the several TNF-family receptors and thereby reasonably predict which conserved amino acids are required for ligand binding.

Furthermore, at the time of filing, the TNF-family ligand TRAIL had been isolated and characterized. See specification at page 3, line 22 through page 4, line 15, and the cited references therein. Accordingly, the TRAIL ligand was readily available for use in ligand binding assays. The specification further teaches: methods to screen for ligand binding (page 31, line 3 through page 32, line 28), conservative amino acid substitutions (page 23, line 37 through page 25), and methods of mutagenesis to generate polypeptides with amino acid substitutions (page 25, lines 4-13). Given the high level of skill in the art regarding the structure of TNF-family receptor ligand binding domains, and the teachings in the specification as to which amino acids must be conserved, methods to make conservative substitutions, and how to test for TRAIL binding, it would be a simple matter of routine experimentation for one of ordinary skill in the art to determine which polynucleotides actually encode a polypeptide capable of binding TRAIL. Since the skilled artisan has clear guidance as to which polynucleotides predictably will encode



a polypeptide that will bind a TNF-family ligand, and only routine experimentation is required to screen for TRAIL binding, the possibility that some polynucleotides embodied by the claims would not encode such a polypeptide does not defeat enablement.

Therefore, the specification is fully enabling for the polynucleotides recited in claims 53, 126, and 194.

Claim 127, as amended, recites a polynucleotide comprising a first nucleic acid at least 90% identical to a second nucleic acid encoding the mature amino acid sequence encoded by the cDNA clone in ATCC Deposit No. 97853, wherein the first nucleic acid encodes a polypeptide which induces apoptosis. The Examiner has stated that Example 5 provides enablement for the full-length receptor inducing apoptosis. *See* Paper No. 12 at page 6, *see also*, Figure 5 and page 8, lines 7-10 of the captioned application. Upon expression in eukaryotic cells, a full-length cDNA clone contained in ATCC Deposit No. 97853 would express the mature DR4 amino acid sequence on the surface of the cells. Since claim 127 recites certain polynucleotides which encode the mature DR4 polypeptide, claim 127 includes specific embodiments which are enabled by disclosure of the present application.

Applicants further submit that claim 127 is enabled for its full scope using the rule set out in *Atlas Powder* and *Wands*. Given (a) the teachings of the present application, and (b) the high level of skill in the art regarding TNF-family receptor death domains, one of ordinary skill in the art could routinely make and use the claimed polynucleotides which encode polypeptides which induce apoptosis, without undue experimentation.

The specification teaches, at page 2, line 1 to page 3, line 21, and in the references cited therein, that a great deal is known about the death domains of TNF-family receptors. Figure 2 shows a comparison of the amino acid sequences of four different TNF-family receptors, including

DR4, which illustrates conserved amino acid regions throughout the respective polypeptides, including the death domain regions important for induction of apoptosis. Accordingly, one of ordinary skill in the art could compare the deduced amino acid sequences of the several TNF-family receptors which induce apoptosis, and in particular, the death domains, to reasonably predict which conserved amino acids are required for the induction of apoptosis.

The specification further teaches: a method to screen for apoptosis (Example 5), conservative amino acid substitutions (page 23, line 37 through page 25), and methods of mutagenesis to generate polypeptides with amino acid substitutions (page 25, lines 4-13). Given the high level of skill in the art regarding the structure of TNF-family receptor death domains, and the teachings in the specification as to: which amino acids should be conserved in the death domain and elsewhere in the polypeptide; methods to make conservative substitutions; and how to test for apoptosis; it would be a simple matter of routine experimentation for one of ordinary skill in the art to determine which polynucleotides encode polypeptides which induce apoptosis. Since the skilled artisan has clear guidance as to which polynucleotides will encode a polypeptide that will induce apoptosis, and only routine experimentation is required to screen for apoptosis, the possibility that some polynucleotides embodied by the claims would not encode such a polypeptide does not defeat enablement.

Therefore, the specification is fully enabling for the polynucleotides recited in claim 127.

Claims 89 and 102, as amended, recite isolated polynucleotides comprising a first nucleic acid at least 90% identical to a second nucleic acid encoding various polypeptide fragments of SEQ ID NO:2, wherein a DR4 variant consisting of amino acids 24 to 468 of SEQ ID NO:2, with the exception that amino acids 265-468 of SEQ ID NO:2 (in claim 89) or amino acids 379 to 422 of SEQ ID NO:2 (in claim 102) are deleted and replaced with a polypeptide encoded by said first

nucleic acid, induces apoptosis *in vitro* when over-expressed in human 293 embryonic kidney cells. One of ordinary skill in the art would readily understand from the specification and the art existing at the time of filing that a mature DR4 polypeptide comprising the claimed polypeptide fragment would have to include a death domain. For example, the nucleic acid would be related to a fragment of the polynucleotide comprising nucleotides 1153-1284 of SEQ ID NO:1, which encodes the DR4 death domain. As noted above in the remarks relating to claim 127, additional structural features required for the induction of apoptosis in the DR4 variant comprising the polypeptide can be predicted based on the existing art and the disclosure provided in the present application. The specification further discloses the routine experimental methods to screen for apoptosis *in vitro* by overexpression in human 293 embryonic kidney cells. Therefore, one of ordinary skill in the art could easily discern those polynucleotides encompassed by claims 89 and 102 which encode a polypeptide which, when substituted into a DR4 variant, will allow that DR4 variant to induce apoptosis in the stated *in vitro* test. Since the skilled artisan has clear guidance as to which DR4 variants comprising the claimed polypeptide will induce apoptosis, and only routine experimentation is required to screen for apoptosis in the stated *in vitro* test, the possibility that some polynucleotides embodied by the claims would not encode such a polypeptide does not defeat enablement.

In view of these remarks, Applicants respectfully request that the Examiner reconsider and withdraw all rejections under 35 U.S.C. § 112, first paragraph, as applied to the pending claims.

***Rejections under 35 U.S.C. § 102***

The Examiner has rejected claim 157 under 35 U.S.C. 102(a) as being anticipated by GenBank Accession No. AA100865. *See* Paper No. 12 at page 8. Applicants respectfully traverse.

The Federal Circuit has stated that "[i]t is axiomatic that for prior art to anticipate under § 102 it has to meet every element of the claimed invention . . . ." *Hybritech Incorporated v. Monoclonal Antibodies, Inc.* 231 U.S.P.Q. 81, 90 (Fed. Cir., 1986). Claim 157 requires that the claimed polynucleotide include a nucleic acid which encodes at least 30 contiguous amino acids from 1 to 238 of SEQ ID NO:2.

The Examiner states that GenBank Accession No. AA100865 is identical to nucleotides 94 to 225 of SEQ ID NO:1, and therefore encodes at least 30 consecutive amino acids of SEQ ID NO:2. However, Applicants respectfully point out that GenBank Accession No. AA100865 is *not* identical to nucleotides 94 to 225 of SEQ ID NO:1, and further does not encode at least thirty consecutive amino acids of SEQ ID NO:2. Specifically, GenBank Accession No. AA100865 has at positions 162 and 163 (as well as numerous other positions) the symbol "N", which indicates that a nucleotide is *probably* present at that position, but its identity could not be ascertained. By placing "Ns" in the ambiguous positions, the authors were not specifically defining that "any nucleotide" could be in those positions, or that they were in possession of a group of polynucleotides with "any nucleotide" in those positions, rather, the authors were stating that in the single-pass sequencing run used to create the EST, they could not ascertain which specific nucleotides, *if any*, belong in those positions. Therefore, upon publication of GenBank Accession No. AA100865, the public was in possession of incomplete sequence information.

Since the sequence is not fully defined, GenBank Accession No. AA100865 does not encode at least 30 amino acids from 1 to 238 of SEQ ID NO:2.

In addition to the numerous ambiguities in the nucleotide sequence, there was no guidance as to which reading frame the sequence should be translated in, or whether the sequence encoded a protein at all. Applicants note that upon translation, all three forward reading frames of GenBank Accession No. AA100865 contain termination codons as well as ambiguous amino acids. Thus, without the hindsight provided by the captioned application, there was no suggestion or teaching in the reference, or elsewhere for that matter, that would have motivated one of ordinary skill in the art to choose to translate any one reading frame over another. Nor was there any teaching of which specific region of any one reading frame to translate as would have been required, since GenBank Accession No. AA100865 also contains at least 5 frame-shifts relative to the similar region of SEQ ID NO:1.

Finally, even assuming, *arguendo*, that a teaching existed which motivated the skilled artisan to translate, in the proper reading frame, the region defined by nucleotides 93 to 224 of GenBank Accession No. AA100865, the resulting codon spanning nucleotides 162-164, namely "NNC," could encode any one of a number of different amino acids depending on the identity of the correct nucleotides in positions 162 and 163. Since the reference provided incomplete information as to the exact nucleotide sequence, one of ordinary skill in the art would have had no way of knowing which amino acid was the correct one.

Therefore, claim 157 is novel and non-obvious over GenBank Accession No. AA100865. Based on these remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(a).

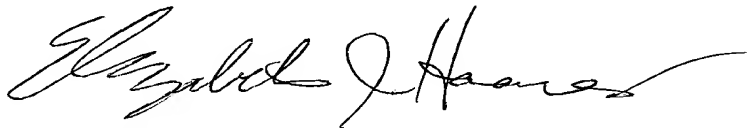
***Conclusion***

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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